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Research Article

Clinical Characteristics and Outcome Associations of Pediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2 in a Brazilian Region

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Abstract

Introduction: Pediatric multisystem inflammatory syndrome (MIS-C) temporally associated with prior infection by SARS-COV-2 has caused great concern in the pediatric community, and requires a better understanding of its presentation, characteristics, and evolution to guide more accurate treatment strategies. This study aimed to identify the epidemiological characteristics, signs, symptoms, and complementary changes in patients notified for MIS-C and relate these findings changes with complications and outcomes. **Methods:** Population-based study with data extracted from the reporting forms from January 2020 to April 2021, from a total of 14 Brazilian hospitals. This study was approved by the Research Ethics Committee of the Federal University of Goiás and was conducted with a non-probabilistic sample of 62 children. SPSS 27.0 software was used for database elaboration and analysis, with a significance level of 5% using the chi-square test or Fisher's exact test. **Results:** Of the 62 patients included, 31 (50.0%) corresponded to male sex, being the median age of 5 years (10 months to 17 years). The gastrointestinal system was the most affected in 83.8% of the cases. Hypotension/shock was the less prevalent diagnostic criterion, occurring in 22 patients (35.5%). Among the echocardiographic findings, valvulite (23.0%) and myocardial dysfunction (20.5%) were the most common. Arterial hypotension with the need for vasoactive drugs occurred in 16 patients (25.8%), noninvasive and invasive mechanical ventilation were used in 20.9% and 6.4%, respectively. There was one death and two cases of sequelae at discharge. **Conclusions:** There was a predominance of gastrointestinal and muco-skin signs supporting the diagnosis; hypotension/shock and cardiac dysfunction were the least observed. Death and sequel to discharge had a statistical relationship with CT with "ground-glass" and mechanical ventilation. Similarly, vasoactive drugs and mechanical ventilation were associated in the multivariate analysis.

Keywords: COVID-19; MIS-C; Epidemiology; Pediatrics.

Introduction

In December 2019, several cases of pneumonia of unknown cause were reported in Wuhan city, China. Subsequently, a beta coronavirus was identified, initially named 2019-nCoV by the World Health Organization (WHO), but also known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). In April 2020, the Pediatric Society of the United Kingdom issued an alert on the condition in children and adolescents called pediatric multisystem inflammatory syndrome (MIS-C), which is characterized by clinical and laboratory abnormalities similar to those of Kawasaki disease, incomplete Kawasaki disease and/or toxic shock syndrome. Similarly, in May of the same year, Verdoni et al. (2020) published an observational cohort showing a 30-fold increase in the incidence of this disease in the Bergamo region of Italy following a high COVID-19 infection rate.

The most plausible pathophysiological mechanism is that a SARS-CoV-2 superantigen (probably at the site of the spike protein, between the S1 and S2 subunits – D839Y/N/E mutation) may trigger a catastrophic activation of the immune response [1] with elevation of IL-17A, IL-6, and CD40 and reduction of T lymphocytes and cytotoxic T lymphocytes. The cytokine storm leads to endothelial injury, with the release of specific endothelial alarmins (S100A12), which induce chemotaxis and recruitment of neutrophils, macrophages and monocytes, prolong inflammation and necrosis, and release autoantibodies against the endothelium [1].

Given the clinical variability and the importance of establishing diagnostic criteria, both the North American regulatory agency (Centers for Disease Control and Prevention - CDC) and the WHO and the UK Royal College of Pediatrics and Child Health have issued diagnostic criteria that use fever and elevated inflammatory markers as mandatory criteria, in addition to signs of multisystem involvement, evidence of exposure to SARS-CoV-2 infection and exclusion of other possible causes. In our country, the Brazilian Society of Pediatrics and the Ministry of Health have adopted the WHO's criteria for the diagnosis of MIS-C, which is why we also used them in the present study.

Regarding treatment, despite the lack of a single global guideline, the implementation of initial stabilization (support for disorders such as dehydration, electrolyte changes and hypoxemia), the treatment of organic disorders (such as shock and cardiac dysfunction, acute kidney injury and respiratory failure) and the specific approach based on the pathophysiological concept of immune dysregulation are postulated [2,3].

The vast majority of patients make a full recovery, with a mortality rate of between 1% and 2% [4]. Despite cardiac involvement in a significant proportion of cases, most patients recover completely if followed up within 90 days [5-7] and a UK cohort also demonstrated resolution of the inflammatory state within six months of the event [8].

Materials and Methods

This is a population-based study with data from the pediatric multisystem inflammatory syndrome (MIS-C) case notification forms issued in 14 Brazilian hospitals from January 2020 to April 2021. The study was approved by the Research Ethics Committee of the Universidade Federal de Goiás (CAAE 50645721.1.0000.5083) in September 2021 prior to data collection.

A non-probabilistic sample of children diagnosed with MIS-C was conducted according to World Health Organization (WHO) criteria, excluding cases that did not meet the specific criteria or had a different diagnosis than MIS-C, or who had inadequate forms completion. SPSS 27.0 software (Statistical Package for the Social Sciences – IBM Corp., Armonk, NY, USA) was used to develop and analyze the database. The significance level was set at 5% and the association between categorical variables was analyzed using the chi-square test or Fisher's exact test.

In this study, the numerical and categorical variables were analyzed. The numerical variables include: Age, time from fever to treatment and duration of hospitalization. The categorical variables were: sex at birth, ethnicity/color, case definition criteria, diagnostic hypotheses at the time of admission, admission to an ICU bed, perceived/reported signs and symptoms, complications encountered, pre-existing illness or condition, contact with a confirmed case of COVID-19, laboratory test results (hemoglobin, total leukocytes, neutrophils, lymphocytes, hematocrit, platelets, activated partial thromboplastin time - aPTT, prothrombin time - PT, fibrinogen, procalcitonin, C-reactive protein, erythrocyte sedimentation rate - ESR, D-dimer, creatinine, sodium, potassium, urea, troponin, lactate dehydrogenase - LDH, alanine transaminase - ALT, aspartate aminotransferase - AST, albumin, lactate, ferritin), imaging examinations (chest X-ray, chest tomography, echocardiogram, abdominal ultrasound), collection and results of RT-PCR and sorology for COVID-19, treatments initiated (antivirals, corticosteroids, immunoglobulin), classification of cases, evolution, consequences upon hospital discharge and confirmation criteria.

Results

A total of 97 pediatric multisystem inflammatory syndrome (MIS-C) report forms temporally related to COVID-19 were

identified for the selected time period. Of these, 35 were excluded from the analysis because they did not meet the criteria for MIS-C, had received a different diagnosis, were still under investigation at the time of the study, or were inadequately completed and contained incomplete data (Figure 1).

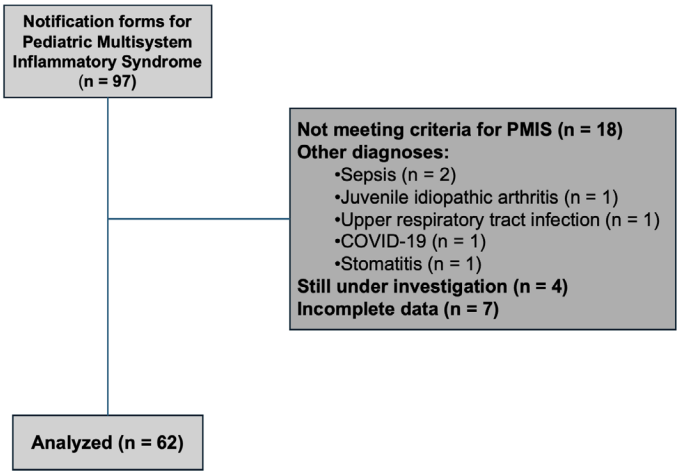

Figure 1: Flowchart for the analysis of the Pediatric Multisystem Inflammatory Syndrome Reporting Forms.

Of the evaluation of confirmed cases, 31 (50.0%) were male, with a mean age of 5 years (between 10 months and 17 years), 30 (48.7%) were brown and 45 (72.5%) were previously healthy.

The gastrointestinal system was the most affected, with signs or symptoms noted in 83.8% of cases, followed by mucocutaneous (82.2%), neurological (70.9%), cardiovascular (58%) and respiratory (48.3%). Other changes are shown as percentages in (Table 1).

Characteristics	**N=62**	**%**
Sex		
Female	31	50,0
Male	31	50,0
Race/Skin color		
White	13	20,9
Curtain	30	48,3
Black	2	3,3
No information	17	27,5
Co-morbidities		
Yes	17	27,5
Signs and Symptoms		
Circulatory and hemodynamic	36	58,0
Edema	24	38,7
Gastrointestinal	52	83,8
Mucocutaneous	51	82,2
Neurological	44	70,9
Oliguria	10	16,1
Respiratory	30	48,3
Altered laboratory markers		
Albumin	34	54,8
Creatinine	13	20,9
LDH	29	46,7
D-dimer	45	72,5
Ferritin	42	67,7
Fibrinogen	20	32,2
Hemoglobin	43	69,3
Leukocytes	31	50,0
Platelets	40	64,5
Potassium	13	20,9
C-reactive protein	56	90,3
Sodium	18	29,0
ALT	32	51,6
AST	32	51,6
PT	28	45,1
Troponin	8	12,9
aPTT	20	32,2
Urea	11	17,7
ESR	48	77,4
Positive COVID-19-specific laboratory tests		
RT-PCR	19	30,6
Sorology	22	35,4

Treatment		
Anticoagulants	35	56,4
Corticosteroids	31	50,0
Immunoglobulin	55	88,7
Confirmation criteria for COVID-19		
Clinical-epidemiological	10	16,2
Laboratory	52	83,8
Complications		
Seizures	3	4,8
Hypotension (need for vasoactive medication)	16	25,8
Acute Kidney Injury	2	3,2
Need for invasive mechanical ventilation	4	6,4
Need for non-invasive mechanical ventilation	13	20,9
Pneumonia	7	11,3
Hospitalization in ICU		
Yes	41	66,1
Evolution		
Discharged	58	93,5
Death	1	1,6
Unknown	3	4,9

Table 1: *Personal, clinical, laboratory and hospital characteristics of children with Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19; LDH: lactate dehydrogenase; ALT: alanine transaminase; AST: aspartate aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time; ESR: erythrocyte sedimentation rate.*

Fever is an obligatory sign of the syndrome and all cases were recorded with this sign occurring a median of 4 days prior to treatment. Another consistently present criterion in this series was the elevation of inflammatory markers. On the other hand, hypotension/shock occurred in only 22 patients (35.5%). C-reactive protein and erythrocyte sedimentation rate were altered in most patients (90.3% and 77.4%, respectively), as were albumin (54.8%), D-dimer (72.5%), ferritin (67.7%) and hemoglobin (69.3%).

Regarding imaging studies, some modalities were performed in 55 (88.7%) patients. Echocardiography was performed in almost three-quarters of these cases, followed by chest X-ray (56.3%), abdominal ultrasound and chest tomography (23.7% each). Among the echocardiographic findings, valvulitis and myocardial dysfunction were the most common. Infiltrates, pleural effusions, ground-glass and condensation were found on chest X-ray and computed tomography in more than half of the patients examined.

Hypotension requiring vasoactive drugs occurred in 16 patients (25.8%), and noninvasive and invasive mechanical ventilation was used in 20.9% and 6.4%, respectively. In terms of therapies initiated, 55 (88.7%) of patients received immunoglobulins, 31 (50%) corticosteroids and 35 (56.4%) anticoagulants. The mean time between the onset of fever and gamma globulin administration was 8.13 days (SD±9.8) and ranged from 1 to 66 days. In 66.1% of cases, admission to the intensive care unit occurred with a median length of stay of 7 days, and 1 (1.6%) death was recorded. Two children had sequelae on discharge from hospital (valvulitis and coronary anomalies).

The only death occurred in an adolescent aged 17 years and 7 months; the other 58 children whose survival was confirmed had a mean age of 6.45 years (SD ± 4.35) – p=0.014 (Student's t-test). Multiple regression (multivariate analysis) adjusted for mechanical ventilation (3-59) yielded a p of <0.000001, the same interpretation for the use of vasoactive drugs (Mantel-Haenszel chi-square) (Table 2).

Clinical-laboratory or therapeutic variable		**Associated variable**		**p**
Description	**Total (yes/no)**	**Description**	**Present (yes/no)**	
Mechanical ventilation	62 (3/59)	Death or sequelae	3 (2/1)	0,007*
“Ground-glass” chest CT scan	62 (2/60)	Death or sequelae	3 (2/1)	0,004*
High Ferritin	62 (42/20)	ICU admission	41 (34/7)	0,04*
High lactate	62 (10/52)	ICU admission	41 (10/31)	0,15*
“Ground-glass” chest CT scan	62 (2/60)	ICU admission	41 (4/37)	0,10*
Use of EV Gamma Globulin	62 (55/7)	ICU admission	41 (39/2)	0,14*
Multivariate Analysis for Mechanical Ventilation	62 (3/59)			<0.000001§
Multivariate Analysis for Vasoactive Drugs	62 (16/46)			<0.000001§

Table 2: Analysis of clinical and laboratory variables with unfavorable outcomes (mechanical ventilation, complications, admission to the Intensive Care Unit, sequelae, and evolution to death).

Discussion

In the 62 cases analyzed, an equal distribution between the sexes was identified, a fact not common in other studies in which there was a male predominance [5,9-12].

The median age of 5 years is similar to that identified in a Brazilian study [13-15] although it differs from the trend described in most studies, in which there is a predominance of older age [5,9,11,12,14,18,21]. In addition, older age was statistically relevant in our study compared to death, and this feature may have contributed to the result of the present study. The presence of younger children in our sample can also be considered a consequence of greater suspicion by the local health care system, which identifies cases in a more sensitive manner, and may also represent the presence of other confounding conditions, such as sepsis itself.

As identified in other studies, there is a higher prevalence of brown race/color and although there is yet no genetic explanation – environmental factors and social inequalities are highlighted [15,22]. In terms of medical conditions, 27.5% of patients had a related medical condition, with respiratory and neurological conditions being most cited alongside obesity. This shows a similarity with other studies where the presence of disease is

described in up to 45% of cases, also with a focus on obesity [5,10,12,14-19].

As it is a syndrome, there are numerous possible clinical presentations among signs, symptoms, laboratory, and imaging tests. However, in agreement with other authors [5,9-12,14-23], a predilection for gastrointestinal and mucocutaneous involvement has been noted. This fact proves to be one of the distinguishing features between MIS-C and Kawasaki disease, as in the latter the predominantly younger patients show almost no gastrointestinal signs or symptoms. There are also fewer respiratory symptoms and acute kidney injury in our sample, in contrast to the findings of Relvas-Brandt et al. (2021), who described a sample with higher severity and mortality in which these systems were more frequently affected. This factor may have influenced our result.

Regarding cardiovascular involvement, 25.8% of the sample had hypotension requiring vasoactive medication. When analysing the categorical variables related to the signs, symptoms and investigations of these systems, it was found that myocardial dysfunction on echocardiography had statistical relevance to the use of these drugs. Other studies with a higher frequency of cardiac dysfunction changes on echocardiography also showed a higher need for vasoactive hemodynamic support, confirming the association relationship [14,16,18,21]. On the other hand, it was not possible to correlate changes in biomarkers of cardiac function or tachycardia with complications or even outcomes.

The authors of a study [12], on laboratory findings associated changes in albumin with greater severity of clinical conditions, a trend that was not seen in the present study when evaluating changes in this test with the development of hypotension and the use of vasoactive drugs. Lactate levels also showed no statistical association. On the other hand, ferritin levels were clinically and statistically significant and were associated with a higher risk of ICU admission.

Echocardiography was performed in 70.9% of the cases analyzed, of which the majority (69.2%) showed an alteration. Despite this high incidence, only two patients maintained it at the time of hospital discharge, which is consistent with the postulate of other authors about the good prognosis of structural and functional cardiac changes [5,15,18,19].

To evaluate pulmonary involvement, 67.2% underwent chest X-rays or computed tomography, with alterations found in up to 76.9%. Of these, ground-glass imaging stands out in almost one-third of the CT scans, presenting, in turn, a statistical relationship with evolution in invasive and noninvasive mechanical ventilation, in addition to lethal outcome or the presence of sequelae at discharge.

There is still no uniform treatment for MIS-C, and there are divergences between societies and guidelines, that is reflected in the different approaches of the studies evaluated. In general, immunosuppressive therapy, anticoagulation and antibiotic therapy are most commonly used [5,9-12,14-23]. With some reports of antiviral therapy [15-17]. Almost 90% of the sample studied used immunoglobulins, and more than half received corticosteroids or anticoagulants. Regarding the impact of these drugs on clinical outcome, patients requiring immunoglobulins and corticosteroids were no more likely to be admitted to the ICU.

Of the entire sample, 41 patients were admitted to the ICU, representing 66.1%, and 6.4% of all cases required invasive mechanical ventilation. Only one death was recorded, which was highlighted due to the statistical relationship found with age, use of mechanical ventilation and, as previously mentioned, ground-glass chest tomography.

To our knowledge, a population-based study with these characteristics has not yet been conducted in the region described, and the multicenter observation and longitudinal follow-up until hospital discharge are factors that strengthen this study. The main limitation is the possible incomplete or inadequate completion of the reporting form and an error in the description of the medical record.

Conclusion

This population-based study allowed the inclusion of a substantial number of children and adolescents with MIS-C, evaluating 14 hospitals providing pediatric care. At initial diagnosis, gastrointestinal and mucocutaneous signs predominated, while hypotension/shock and cardiac dysfunction were less common. Unfavorable outcomes such as death (one patient) and sequelae at discharge were related to the presence of a ground-glass pattern on chest CT scans and the need for mechanical ventilation.

Ethical Considerations

This study complied with the principles of Resolution CNS/MS 466/2012 and was submitted for approval by the Ethics Committee for Research of the Hospital das Clínicas da Universidade Federal de Goiás on the Brazilian platform at CAAE: 50645721.1.0000.5083 and endorsed on September 21, 2021.

Conflict of Interest

No conflict of interest.

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